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EXAMINER	
KRASS, FREDERICK F	

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1614	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/092,508	Applicant(s) BISSERY, MARIE-CHRISTINE	
	Examiner Frederick Krass	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2,3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Election of Species Requirement

The election of species requirement is, upon reconsideration in light of the state of the prior art found in searching the case, withdrawn.

Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following precedent is believed relevant to the instant case.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed.Cir.1997), *cert. denied,* 523 U.S. 1089, 118 S.Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has

adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed.Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia,* "functional characteristics *when coupled with a known or disclosed correlation between function and structure* ...." *Enzo Biochem, Inc. v. Gen-Probe Inc.,* 296 F.3d, 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed.Reg. at 1106 (emphasis added)). Moreover, although Eli Lilly and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp.2d 216, 225 (W.D.N.Y. 2003).

Specifically, the term "stilbene derivative" in claim 1 is not supported by an adequate written description. The instant specification does not adequately show that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, such as by structure, formula, chemical name, or physical properties. Instead, it discloses only the limited genus of combretastatins, as exemplified by the structural formulae provided at pages 5, 8 and 9. No correlation between anticancer function and any other stilbene "derivatives" is provided or established.

Scope of Enablement Rejection

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of carcinomas, does not reasonably provide enablement for the treatment of "solid tumors" generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art

The claimed invention relates to chemotherapy, and the relative skill of those in the art is high, generally that of a PHD or MD. This unpredictability has a number of facets, as discussed hereinafter.

A. Treatment by Cancer Type

While the state of the art is relatively high with regard to the treatment of specific cancers with specific agents, it has long been underdeveloped with regard to the treatment of cancers broadly. In particular, there is no known anticancer agent which is effective against all cancers. This is why the National Cancer Institute (NCI) has the extensive *in vitro* drug screening program it does. As discussed by the court in In re Brana, 51 F.3d 1560 (Fed. Cir. 1995), *in vitro* assays are used by NCI (such as the P388 and L1210 lymphocytic leukemia tests at issue therein) to measure the potential antitumor properties of a candidate compound. Brana at 1562-63. If success is shown in this initial screening step, this demonstrates that at least one cancer type (e.g., lymphocytic leukemia) is sensitive thereto, and provides the incentive to select it for further studies to determine its usefulness as a chemotherapeutic agent against other cancer types (lung, breast, colon, etc.) *Id.* at 1567-68. These *in vitro* tests are considered reasonably correlative of success *in vivo*.

Thus, a considerable amount of *in vitro* empirical testing is required, with no *a priori* expectation of success being present, before a candidate anticancer agent can be considered useful against any particular cancer type.

B. Combination Chemotherapy

Furthermore, the unpredictability observed with single agents is compounded when a combination of agents is used. This is summarized by WO 00/61142, at page 1, lines 17-23:

> Combination therapies, while desirable, are a hit or miss proposition. The treatments are typically not additive. In many cases, cross effects and treatment load can result in lower effectiveness for the combinations, than either treatment alone.

This is verified by U.S. Pat. 6,465,448 at col. 1, lines 56-59:

> The design of drug combinations for the chemotherapeutic treatment of cancer should be approached with the goals of 1) finding a combination that is synergistic with and not merely additive to the first compound with respect to the elimination of the tumor, and 2) finding a second drug that does not potentiate the toxic effects of the first therapeutic agent. *These conditions require a great deal of empirical testing* of agents known to have anticancer properties with agents that either may have anticancer properties, or that may augment the first agent in other ways. (Emphasis added).

Thus, when two (or more) agents are used, even more additional empirical testing is required, again with no *a priori* expectation of success.

2. The breadth of the claims

The claim is very broad and inclusive of "solid tumors" generally.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction for ascertaining, *a priori*, which solid tumors will respond to treatment.

4. The quantity of experimentation necessary

The lack of adequate guidance from the specification or prior art with regard to the actual treatment of all cancers in a mammal with the claimed compounds fails to rebut the presumption of unpredictability extant in this art. Applicants fail to provide the guidance and information required to ascertain which particular type of cancer the claimed anticancer agent will be effective against without resorting to undue experimentation. Applicant's limited disclosure of the treatment of carcinomas (see the fifth line from the bottom of page 20) is noted but is not sufficient to justify claiming all cancers broadly.

Absent a reasonable *a priori* expectation of success for using a specific chemotherapeutic agent/combination to treat any particular type of cancer, one skilled in the art would have to extensively test many various tumor types. Since each prospective embodiment, and indeed future embodiments as the art progresses, would

have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would be required to practice the invention as its is claimed in its current scope, because the specification provides inadequate guidance to do otherwise.

Anticipation Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1) Claims 1-3 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Morinaga et al (USP 6,462,087 B1).

Patentees disclose the use of pharmaceutical compositions comprising the combretastatin recited by instant claim 3 in combination with platinum coordination compounds (i.e. alkylating agents) to treat solid tumors (column 2, line 43; see also working example 1 at col. 10).

2) Claims 1 and 2 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (WO 02/056682 A1).

Patentees disclose pharmaceutical compositions comprising combretastatins and additional anticancer agents (see the list spanning pages 12-14, and the specific combinations exemplified at pages 28-30).

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al in view of Hatanaka et al (USP 5,674,906).

The primary reference discloses pharmaceutical compositions comprising combretastatins and additional anticancer agents including alkylating agents (page 12, lines 14-21), doxorubicin (page 13, line 36), vincristine (page 14, line 7) and antimetabolites (page 13, lines 21-29). Taxanes such as paclitaxel/docetaxel may also be used (page 14, lines 5 and 6). Although the reference does not specifically disclose taxotere, the use of that particular compound would surely have been obvious from the prior art disclosure at page 14, lines 5 and 6, whose non-limiting nature would reasonably suggest to and motivate the skilled artisan to use such a well-known, widely and commercially available species. Various solid tumors may be treated (see page 16).

The primary reference differs from the instant claims insofar as the particular combretastatin derivative recited by instant claim 3 is not specifically disclosed. It does clearly teach, however, that combretastatin derivatives may be used "without limitation" (page 9, lines 21-25).

The secondary reference teaches that the particular combrestatin derivative of instant claim 3 (see especially the second compound at columns 21 and 22) have unusually high carcinostatic activity, coupled with unusually low toxicity (column 1, lines 27-36). It differs from the instant claims insofar as the use of additional anticancer agents therewith is not specified.

It would have been obvious to have used the combretastatin derivative of instant claim 3 to treat solid tumors, combined with another anticancer agent as disclosed by the primary reference, motivated by the desire to obtain the increased activity and lowered toxicity associated with that derivative as taught by the secondary reference.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (703) 308-4335. The examiner can normally be reached on Monday, Tuesday and Thursday from 9am to 5pm, and on Fridays from 11am to 7pm. The examiner is off Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached at (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0193.

Frederick Krass
Primary Examiner
Art Unit 1614